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REMARKS

In the latest Office Action, the previous rejections under 112, second paragraph and Section 103 have been withdrawn. Claims 21 and 26 are newly rejected under 35 USC Section 112, first paragraph. Claim 25 is objected to for depending from a rejected claim. In order to obviate the objection, claim 25 is incorporated in claim 21 without prejudice or disclaimer. Hence the cancellation of claim 25 herein as moot. Claims 27 to 31 are added herein with support for these claims being found at least as follows: claim 27 (page 4, lines 22-23); claim 28 (page 6, lines 12-14 and the examples); claim 29 (claim 9); claim 30 (claim 10); and claim 31 (claim 21, and page 15, line 16 through to line 2 on page 16).

In the sole (newly raised) rejection, claims 21 and 26 are rejected under 35 USC Section 112, first paragraph, on the basis that the specification, while being enabling for methods where the HER2 antibody is huMAb4D5-8, does not reasonably provide enablement for methods for identifying and treating patients disposed to respond favorably to any HER2 antibody. The Examiner urges that the basis for the claimed methods is that the specification provides data showing that those patients having her2 amplification respond favorably to HERCEPTIN® when compared to patients who do not have her2 gene amplification. The Examiner further urges that "there are no teachings in the prior art demonstrating an association between HER2 status (either protein overexpression or gene amplification) and a favorable response to HER2 antibodies other than HERCEPTIN®;" that the mechanism by which HERCEPTIN® causes regression of breast tumors is not completely understood; and that there appears to be some HER2 antibodies (e.g. 2C4) that are effective on breast tumors that express normal levels of HER2 and do not overexpress HER2. The Examiner additionally asserts that the prior art fails to demonstrate an association between favorable outcome with any other HER2 antibody and her2 gene amplification, and that undue experimentation would have to be done by a skilled worker to discover if an association exists between favorable response to treatment with a HER2 antibody and gene amplification.

Applicants submit that the presently claimed invention is enabled for HER2 antibodies including, but not limited to, HERCEPTIN®. Claim 31 herein concerns therapy of patients with her2 gene amplification with a "a HER2 antibody which inhibits cellular proliferation of HER2-overexpressing human breast tumor cells." As explained at pages 15-16 of the present application, 4D5/HERCEPTIN® is a HER2 antibody which inhibits cellular proliferation of HER2-overexpressing human

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breast tumor cells. The prior art, including Hudziak et al. *Mol. Cell Biol.* 9(3): 1165-1172 (1989) and US Patent No. 5,677,171, described in the specification, provides detailed guidance on making and screening for antibodies, like 4D5, which inhibit cellular proliferation of HER2-overexpressing breast tumor cells. For example, Table 1 of Hudziak et al. (1989), of record, discloses several antibodies which inhibit such proliferation. Columns 18-19 of US Patent No. 5,677,171 also disclose several growth inhibitory HER2 antibodies. Applicants submit that, by May 2000, the skilled person could have used the other growth inhibitory HER2 antibodies as disclosed in Hudziak et al. and US Patent No. 5,677,171, or yet further growth inhibitory HER2 antibodies which could have been made and screened for based on the guidance provided by the cross-referenced art, in the presently claimed methods.

Turning now to the specific bases of the rejection, and first whether teachings in the prior art demonstrated an association between HER2 status (either protein overexpression or gene amplification) and a favorable response to HER2 antibodies other than HERCEPTIN®. Applicants submit that, US Patent No. 5,677,171, for example, discloses antibodies, other than 4D5, in particular 3E8, which inhibited proliferation of HER2-overexpressing tumor cells *in vitro* and *in vivo* (columns 18-19). Hence, Applicants submit that US Patent No. 5,677,171, cited in the present application at page 15, demonstrated an association between HER2 status and a favorable response to HER2 antibodies, including but not limited to HERCEPTIN®.

As to the Examiner's second concern, that the mechanism by which HERCEPTIN® causes regression of breast tumors is not completely understood, Applicants submit that a complete understanding of the mechanism is not required in order to make and use antibodies, other than HERCEPTIN®, that inhibit cellular proliferation, in the presently claimed methods. Since the methodology for selecting growth inhibitory HER2 antibodies was established at the time of filing the present application, the skilled person could have made and selected another growth inhibitory HER2 antibody, without having to understand why it was. Such "why" information, while interesting from a scientific standpoint, is not needed to practice the presently claimed methods with antibodies other than HERCEPTIN®.

Applicants now address the Examiner's statement that there appear to be some HER2 antibodies (e.g. 2C4) that are effective on breast tumors that express normal

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levels of HER2 and do not overexpress HER2. Nahta and Esteva, relied on by the Examiner, explain on page 5080, that "Altering HER-2 heterodimers has the potential to block compensatory signaling in HER-2-overexpressing tumor cells treated with trastuzumab and inhibit signaling in cells that express normal levels of HER-2. Phase I clinical trials of 2C4 in breast cancer are currently being conducted and include patients whose tumors express normal HER-2 levels." (emphasis added). Hence, this reference does not teach that the HER2 antibody 2C4 is ineffective in HER2 overexpressing cancers, rather that it can be used to treat tumors that overexpress HER2 as well as those which express HER2 at normal level. Indeed, Agus et al. *Cancer Cell* 2:127-137 (2002) (copy to follow in IDS), cross-referenced in Nahta and Evesta, demonstrate that 2C4 inhibits the growth of both low- and high-HER2 expressing breast cancer *in vivo* (Fig. 3E, and column 1 on page 131 of Agus et al.). This evidence indicates that HER2 antibodies other than 4D5/HERCEPTIN®, including 2C4, are effective on breast tumors that overexpress HER2.

Applicants have addressed the bases of the Examiner's rejection and shown that the skilled person, by the year 2000, could have treated a breast cancer patient with growth inhibitory HER2 antibodies other than 4D5/HERCEPTIN®. Applicants have explained that such antibodies, including 3E8 or 2C4, as well as yet other HER2 antibodies that could have been identified based on the teachings available in the art, could have been used to practice the presently claimed methods.

In addition, the present application describes and enables methodology for identifying a breast cancer patient disposed to respond favorably to a HER2 antibody by detecting her2 gene amplification in tumor cells in a tissue sample from the patient. Techniques for detecting her2 gene amplification are described at pages 5-6, 17-22, the examples, and elsewhere throughout the disclosure, for instance. Hence, the specification clearly enables the identification of human breast cancer patients with her2 gene amplification for therapy.

Moreover, the specification describes how to treat those patients with growth inhibitory HER2 antibodies at pages 22-26 and in the examples, for instance. Thus, the specification further enables treating a patient having her2 gene amplification with a HER2 antibody in an amount effective to treat the patient's breast cancer.

The Examiner contends that further undue experimentation would have to be done

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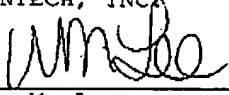
by a skilled worker to discover if an association exists between favorable response to treatment with a HER2 antibody and gene amplification. No evidence is provided by the Examiner to show that the correlation between her2 amplification and clinical responses provided by the present application would not pan out for other growth inhibitory HER2 antibodies. Applicants submit that, based on the data showing the clinical outcomes of patients with her2 amplification treated with HERCEPTIN®, the skilled person could successfully practice the invention for other HER2 antibodies and that such experimentation would not be undue. In the absence of any evidence demonstrating the method would not work for other antibodies, Applicants submit that the enablement rejection must fall, particularly in view of the evidence provided above regarding other growth inhibitory HER2 antibodies.

Applicants respectfully request reconsideration and withdrawal of the Section 112, first paragraph rejection.

Applicants believe that this application is now in condition for allowance, and look forward to early notification to that effect.

Respectfully submitted,  
GENENTECH, INC.

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By:   
Wendy M. Lee  
Reg. No. 40,378  
Telephone: (650) 225-225-1994